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Ab Externo SIBS Microshunt with Mitomycin C for Open-Angle Glaucoma

Three-Year Results as a Primary Surgical Intervention

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Purpose: To determine the effectiveness, risk factors for surgical failure, and adverse events in a large cohort of patients receiving stand-alone ab externo poly(styrene-block-isobutylene-block-styrene) (SIBS) microshunt implantation with mitomycin C (MMC) over 3 years of follow-up.

Design: Retrospective, interventional case series.

Participants: Glaucomatous eyes on maximally tolerated medical therapy with no previous subconjunctival glaucoma surgery.

Methods: Records of eyes that underwent ab externo SIBS microshunt with MMC between July 2015 and November 2017 were reviewed. Data from all follow-up visits were utilized and included intraocular pressure (IOP), medication use, postoperative interventions, complications, and reoperations.

Main Outcome Measures: The primary outcome was proportion of eyes at 3 years with (1) no 2 consecutive IOPs $>$ 17 mmHg (or $<$ 6 mmHg with $>$ 2 lines of vision loss from baseline); (2) $\geq$ 20% reduction from baseline IOP; and (3) using no glaucoma medications (complete success). Secondary outcomes included 14 and 21 mmHg upper IOP thresholds with and without $\geq$ 20% IOP reduction from baseline, qualified success (with glaucoma medications), risk factors for failure, median IOP/medications, postoperative interventions, complications, and reoperations.

Results: One hundred fifty-two eyes from 135 patients were included. Complete and qualified success was achieved in 55.6% and 74.8% of eyes, respectively. Time to first glaucoma medication use was a median of 16.9 (interquartile range [IQR], 12.1−34.1) months; however, 59.4% of eyes remained medication free at 3 years. Significant risk factors for failure included receiving $<$ 0.4 mg/ml of MMC (adjusted hazard ratio [HR], 2.42; 95% confidence interval [CI], 1.44−4.05) and baseline IOP $<$ 21 mmHg (adjusted HR, 1.79; 95% CI, 1.03−3.13). The most common complications were choroidal detachment, hyphema, and anterior chamber shallowing, occurring in 7%, 5%, and 5% of eyes, respectively. The needling rate was 15.1%, with significantly higher frequency for baseline IOP $>$ 21 mmHg (HR, 3.21; 95% CI, 1.38−7.48). Revisions occurred in 7% of eyes and reoperations in 2.6%. Eyes receiving $<$ 0.4 mg/ml of MMC underwent more revisions (odds ratio, 4.9; 95% CI, 1.3−18.3).

Conclusions: Three-year follow-up data from this large cohort continues to support promising rates of qualified and complete success, with decreased medication burden postoperatively and few postoperative complications and interventions. Comparisons to other filtering surgeries will further facilitate integration of the SIBS microshunt into the surgical treatment paradigm.

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Managing patients with glaucoma is a delicate balance between minimizing the risk of treatment-related adverse events and maximizing visual field preservation through adequate reduction of intraocular pressure (IOP). Topical glaucoma medications, particularly those with preservatives, can damage the ocular surface over time, and many patients eventually become refractory to medical treatment.[1] Progressing to surgical management is often required and traditionally carries additional risks. Despite the introduction of several new glaucoma surgeries over the past decade, trabeculectomy remains one of the most commonly performed glaucoma surgeries.[2]

Trabeculectomy very effectively lowers IOP; however, it can be associated with a high postoperative complication rate and requires highly involved postoperative management.[3] Microinvasive glaucoma surgeries were developed to

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alleviate many of these added risks with improved safety profiles and minimal impact on patients' quality of life.[4,5] Schlemm's canal microinvasive glaucoma surgery provides an extremely high safety profile; however, it achieves modest IOP reduction compared with traditional glaucoma procedures.[6] Recently, microinvasive bleb surgeries have emerged that demonstrate greater IOP lowering potential compared with Schlemm's canal microinvasive glaucoma surgeries while at the same time retaining many of the safety benefits and reduced postoperative management requirements compared with traditional glaucoma surgeries.[7]

The PreserFlo microshunt is a microinvasive bleb surgical device composed of bioinert poly(styrene-block-isobutylene-block-styrene) (SIBS) material and has 2 radial fins designed to help seat the device within a scleral tract, mitigating peritubular flow and device migration. The device has a length of 8.5 mm and an internal lumen diameter of 70 μm that functions to regulate outflow and minimize hypotony.[8] Previous studies report promising early safety and efficacy data.[9–14] However, to date, the only reported long-term clinical outcomes extending past 2 years come from a single cohort of 23 patients followed to 5 years.[12] There also still exists some controversy as to the optimal intraoperative mitomycin C (MMC) concentration for the procedure, with previous studies employing concentrations anywhere from 0.2 to 0.5 mg/ml. Recently, a prospective study comparing the 1-year outcomes of the SIBS microshunt vs. trabeculectomy found a higher success rate with a lower mean IOP in the trabeculectomy group but fewer postoperative complications and interventions in the SIBS microshunt group.[15] It is of note, however, that the SIBS microshunt group had significantly more Black patients compared with the trabeculectomy group, and the study used 0.2 mg/ml intraoperative MMC, both of which may have influenced the reported results.

The present study is a continuation of our previous report on 1-year clinical outcomes[14] and presents 3-year outcomes from a large sample of open-angle glaucoma patients with no prior filtering surgery who underwent SIBS microshunt implantation with intraoperative MMC concentrations ranging from 0.2 to 0.5 mg/ml. Our aim was to summarize longer-term efficacy, risk factors for failure, and adverse events associated with stand-alone implantation of the SIBS microshunt with varying MMC concentrations as a primary surgical intervention over a 3-year follow-up period.

Methods

This study reports 3-year outcomes, or longer where available, from an investigator-initiated, single-center, retrospective interventional case series of consecutive patients undergoing ab externo SIBS microshunt implantation with MMC between July 1, 2015 and November 1, 2017. All surgeries were performed by a single surgeon and directly supervised clinical fellows practicing within an academic ophthalmology center in the Greater Toronto Area, Canada. This study adhered to the tenets of the Declaration of Helsinki, and institutional review board approval was obtained from Trillium Health Partners. All patients provided informed consent for surgery. Baseline preoperative characteristics collected include demographics (age, eye, sex, ethnicity, diabetes status) and ocular characteristics: best-corrected visual acuity; IOP at which the decision for surgery was made (preoperative IOP); glaucoma medication classes (in which carbonic anhydrase inhibitors [CAIs] were included); glaucoma diagnosis; cup-to-disc ratio; visual field mean deviation; and history of previous cataract surgery, other ocular surgery, or laser trabeculoplasty.

Inclusion and Exclusion Criteria

The microshunt was implanted in eyes with an IOP above target and/or progressing on maximally tolerated medical therapy. For this analysis, eyes were excluded if they had had prior incisional filtering glaucoma surgery, suprachoroidal stent, retinal surgery, corneal graft surgery, or cyclophotocoagulation; if their glaucoma diagnosis was primary angle closure, uveitic, traumatic, elevated episcleral venous pressure or neovascular; or if surgery was combined with phacoemulsification. Eyes were also excluded if they had less than 1 month of follow-up (out-of-town patients for whom follow-up was not available).

Microinvasive Bleb-forming Surgery with Microshunt Implantation

The procedure for microshunt implantation has been previously described in detail.[14] In summary, under intravenous sedation and topical anesthesia, a traction suture was placed on the cornea, and the surgeon examined the superior conjunctiva to plan the placement of the device. The superonasal conjunctiva was exposed, and 1% preservative-free lidocaine was placed in the sub-Tenon space. A fornix-based conjunctival peritomy was then performed over 2 clock hours. The Tenon layer was dissected carefully, liberating all attachments to the underlying episclera and creating a deep pocket between the superior rectus and medial rectus. Light cautery was applied. Three LASIK merocele sponges (BVI) soaked with MMC were then applied in the quadrant posteriorly between the muscle bellies and anteriorly under the Tenon layer for a total of 2 minutes, carefully avoiding any contact with the limbus. Throughout the study period, MMC dosing was increased in a time-dependent fashion as per increasing surgeon comfort and observed postoperative bleb morphology. Initially, blebs were found to be posterior and diffuse with greater vascularity, leading to the increase in MMC concentration throughout the study period to increase the likelihood of surgical success. For the initial patients, MMC concentrations of 0.2 mg/ml were used, followed by 0.4 mg/ml and 0.5 mg/ml in subsequent patients. Balanced salt solution was then used to irrigate the surface of the eye. A 3-mm mark was then placed posterior from the limbus, and a 1-mm-wide scleral tunnel was made with a microknife entering the anterior chamber (AC) at the trabecular meshwork. A side-port incision was then created. With the use of curved tying forceps, the SIBS microshunt was placed in the tunnel with bevel facing up, and the fins of the device were wedged into the scleral pocket. The position of the device in the AC was inspected to make sure it was sitting just anterior to the iris, and flow through the distal end of the microshunt was then confirmed by injecting balanced salt solution in the AC and pressurizing the eye. If needed, a 23-gauge thin-walled cannula was used to prime the microshunt at the distal end. Tenon's and conjunctiva were then closed in separate layers with 9-0 vicryl suture, ensuring the implant was not caught in the Tenon layer. Subsequently, balanced salt solution was injected in the AC to ensure the presence of a bleb and that no leaks were present.

Postoperative Management

After the procedure, patients were instructed to stop all glaucoma medications and start steroid drops every 2 hours for the first week, followed by a slow taper over 8 to 10 weeks. Topical moxifloxacin drops were used for a week and nonsteroidal anti-inflammatory drops for 1 month. Patients were seen at postoperative day 1, postoperative day 3/4, and then as needed at the surgeon's discretion. All visits included a full biomicroscopy examination and bleb examination. A Seidel test was performed routinely during the first 2 weeks postoperatively. A dilated fundus examination was performed during the first postoperative week and repeated as needed if there were any signs of clinical hypotony. Reintroduction of glaucoma medications, needling, digital ocular compression, AC reformation, surgical revisions, and reoperations were performed as per surgeon discretion. Needling was performed at the slit lamp using a 25-gauge trocar. A total of 0.1 ml of MMC (0.4 or 0.5 mg/ml) was injected before the start of the needling using a long subconjunctival track. After waiting for 20 minutes, and again using a long subconjunctival track, the trocar was used to free the tip of the implant or pierce through the fibrotic capsule as needed. Subconjunctival viscoelastic was injected at the end of the procedure at the surgeon's discretion. After the procedure, topical antibiotics were used for 1 week and steroid drops every 2 hours for the first week, followed by a slow taper over 6 to 10 weeks.

Surgical Revision

Revisions involved a careful dissection of the conjunctiva and removal of the overlying scar tissue. Mitomycin C 0.5 mg/ml soaked in sponges for 2 to 3 minutes, as well as posterior intratissue MMC injection, was used in revision cases. The implant was tested by pressurizing the AC and assessing for flow from the distal end of the microshunt. If any abnormality was noted in the device (poor flow or intraluminal obstruction), the plan was to exchange for a new implant. The distal end of the microshunt was loosely sutured to the sclera. The conjunctiva was closed with 9-0 vicryl, ensuring a tight closure with no leaks.

Primary Outcome

The primary outcome was the proportion of eyes at 3 years achieving complete surgical success. Complete success was defined as: (1) no 2 consecutive IOP readings greater than 17 mmHg, nor clinical hypotony (defined as: IOP less than 6 mmHg with more than 2 lines of vision loss from baseline); (2) at least a 20% reduction from preoperative IOP; and (3) no glaucoma medication use. Qualified success was a secondary outcome that allowed for medication use. Surgical revisions, reoperation, or no light perception vision were considered immediate failures. Out-of-range IOP or medication use in the first month was not considered a failure, nor were in-clinic interventions including needlings at any time during follow-up.

Secondary Outcomes

Secondary efficacy outcomes included upper IOP thresholds of 14 mmHg and 21 mmHg for complete and qualified success criteria with and without a 20% IOP reduction from baseline. Also reported are median IOP and medication burden, time to first medication use, and best-corrected visual acuity in logarithm of the minimum angle of resolution (logMAR) units at last follow-up or at reoperation. In additional secondary analyses, we explored risk factors for failure including sex, age, ethnicity, right vs. left eye, lens status, previous trabeculoplasty, glaucoma type, glaucoma severity, preoperative IOP, preoperative vision, diabetes status, and MMC dose.

Outcomes Based on Preoperative Visual Field Disease Severity

Alternative success criteria were employed based on patient baseline disease severity determined through visual field mean deviation (MD). To be counted as a success, patients with mild disease (MD $>$ -6dB) had to maintain an IOP within 6 to 21 mmHg, patients with moderate disease ($-6 \leq$ MD < -12) within 6 to 17 mmHg, and patients with advanced disease (MD ≤ -12) within 6 to 14 mmHg. Complete success required no glaucoma medication use, and qualified success allowed medication use.

Safety Outcomes

Postoperative interventions, complications (including leak or dehiscence, hyphema, vitreous hemorrhage, choroidal detachments, macular folds, prolonged inflammation, corneal decompensation, macular edema, diplopia, iris incarceration, or blocked or exposed microshunt), more serious complications (including angle closure, retinal detachment, suprachoroidal hemorrhage, malignant glaucoma, blebitis, endophthalmitis, or no light perception vision), and reoperations were recorded and similarly analyzed for risk factors.

Statistical Analysis

All statistical analyses were run on SAS university edition software (SAS Institute Inc). Graphs were drawn with either SAS university edition software or Prism 9 (Version 9.1.2, GraphPad Software, LLC). Categorical variables were displayed as proportions and comparisons were made using a Fisher exact test. Continuous outcomes were described as means (standard deviation) or medians (interquartile range [IQR]) depending on normality, and then compared with either 2-sided *t* tests or Wilcoxon tests as appropriate. All Snellen visual acuity measurements were converted to logMAR. Overall treatment success was calculated using survival analysis to statistically account for loss to follow-up and demonstrated with Kaplan−Meier curves. The results were stratified by the risk factors for failure listed below and again visualized using Kaplan−Meier curves for the various IOP cutoffs for complete and qualified success with the log-rank test used to evaluate differences between strata. Median time to event outcomes were reported and calculated only for those patients experiencing the event within the study period.

Cox proportional hazard models were used to explore risk factors for surgical failure and other adverse events. Baseline and surgical factors were evaluated as potential risk factors on both a univariable (crude) and multivariable (adjusted) basis. The Efron method was used to approximate data with equivalent failure intervals. Collinearity of treatment variables was assessed through a regression model using a Condition Index threshold of > 30. There was assumed to be no competing risk factors that could have affected data censoring. The Martingale residuals method was used to determine if the proportional hazards prerequisites were met for each variable. If a variable did not meet the proportional hazards assumption, this was addressed through either: (1) adding a time-variable interaction term, or (2) stratifying the model by the non-proportional variable. If the regression coefficient of the time-variable interaction term indicates it accounts for less than 1% of the change in hazard over time, the time-variable interaction term was excluded from the final model. To assess for surgeon learning curve impacting the initial surgeries greater than the latter surgeries, an additional Cox proportional hazards model was constructed including a time-of-surgery based variate that compares the hazard associated with the first one-third of surgical cases to the latter two-thirds of cases. Secondary categorical or continuous

Table 1. Baseline Characteristics of Subjects Receiving Microshunt

Demographics	Total, n (%) (N = 152 Eyes)
Age	
Median (IQR), yrs	61 (53–69)
>70 yrs, n (%)	30 (19%)
Left eye, n (%)	76 (50%)
Female, n (%)	65 (42%)
Diabetes, n (%)	20 (13%)
Ethnicity, n (%)	
White	84 (55%)
Non-White	65 (42%)
Vision	
Preop VA (logMAR), median (IQR)	0.18 (0.1–0.3)
Preop BCVA ≥ 0.4 logMAR, n (%)	17 (11%)
Glaucoma type and severity	
Decision IOP, median (IQR)*	20 (16–26)
Medication classes, median (IQR)	4 (3–4)
Cup-to-disc ratio, median (IQR)	0.85 (0.75–0.9)
Preop MD, median (IQR), dB	−11.7 (−19.6 to −3.8)
Disease type	
POAG, n (%)	110 (72%)
PXG, n (%)	11 (7%)
Other OAG, n (%)	16 (10%)
Disease severity, n (%)†	
Mild	35 (23%)
Moderate	31 (20%)
Advanced	85 (55%)
Previous ocular laser/surgery, n (%)	
Cataract surgery	58 (38%)
Laser trabeculoplasty	82 (53%)
iStent	11 (7%)
MMC concentration, n (%)	
0.2 mg/ml	47 (30%)
0.4 mg/ml	83 (54%)
0.5 mg/ml	21 (13%)
Follow-up (mos)	
Median (IQR) follow-up	39.3 (27.8-44.9)
Median (IQR) visit interval	0.90 (0.2-2.9)
Gaps in follow-up, n (%)	
Eyes with >6 mos interval	54 (36%)
Eyes with >9 mos interval	38 (25%)

BCVA = best-corrected visual acuity; IOP = intraocular pressure; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; MMC = mitomycin C; OAG = open-angle glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; VA = visual acuity.
*IOP measured at the visit when the decision was made to proceed with surgery.
†Based on visual field mean deviation: mild = 0 dB to > −6 dB; moderate = −6 dB to > −12 dB; and advanced = −12 dB or worse.

outcomes were analyzed with a general linear model on both a univariable and multivariable basis. As some patients had 2 eyes enrolled, we accounted for intracluster dependence through a frailty model using the approach popularized by Lee, Wei, and Amato (1992),[16] which estimates the regression parameters in the Cox model by maximum partial likelihood estimates under an independent working assumption and uses a robust sandwich covariance matrix estimate. A 2-sided P value of < 0.05 was considered statistically significant.

Results

Study Population and Baseline Characteristics

This study identified 178 eyes without previous glaucoma surgery that underwent stand-alone SIBS microshunt implantation with MMC between July 1, 2015 and November 1, 2017. Twenty-six eyes were non–open-angle glaucoma (primary angle closure, uveitic, traumatic, elevated episcleral venous pressure, or neovascular) and were excluded from the analysis. The final cohort included 152 eyes from 135 patients (Table 1) with a 75.5% follow-up rate over 3 years and a median (IQR) follow-up time of 39.3 (27.8–44.9) months. The distribution of follow-up appointments between the first 6 months and the remainder of the follow-up period was 48.3% vs. 51.7%, respectively, with a total of 2251 postoperative appointments. The median (IQR) visit frequency in the first 6 months was 0.4 (0.17–0.87) months, and over the remainder of the follow-up period was 2.0 (0.67–5.13) months. A comparison of baseline characteristics between patients with complete follow-up and those without complete follow-up is presented in Table S2 (available at www.ophthalmologyglaucoma.org). The mean number of appointments per patient occurring within specified follow-up periods is presented in Table S3 (available at www.ophthalmologyglaucoma.org).

Forty-two percent of patients were female, 55% were White, 58% had a baseline IOP over 21 mmHg, and 55% had advanced disease. Stratifying the patients by MMC dose (a known risk factor for failure based on our previous work[14]) shows overall similar patient populations, with significantly more patients in the ≥ 0.4 mg/ml MMC group (77% vs 23%) receiving previous laser trabeculoplasty.

Primary Outcome

Surgical success at 3 years was defined as no IOP above 17 mmHg or below 6 mmHg (also with clinical hypotony) on 2 consecutive visits and at least a 20% reduction from baseline IOP (Fig 1). Complete success occurred in 55.6% of eyes and qualified success in 74.8% of eyes. For complete success criteria, the median (IQR) time to failure was 10.5 (5.4–23.4) months (n = 67). For qualified success criteria, the median (IQR) time to failure was 16.6 (9.6–28.9) months (n = 38). No failures occurred due to clinical hypotony.

Secondary IOP Outcomes

Using an upper IOP cutoff of 14 mmHg, complete success was achieved in 47.7% of patients. With an upper cutoff of 21 mmHg, 57.0% achieved complete success. Qualified success was achieved in 74.2% and 77.5% for upper cutoffs of 14 mmHg and 21 mmHg, respectively.

Sensitivity Analysis for Primary Outcome

Surgical success at 3 years (Fig S2, available at www.ophthalmologyglaucoma.org) was defined using IOP cutoffs of ≥ 6 mmHg and ≤ 14, 17, and 21 mmHg, without the requirement for a 20% reduction from baseline IOP. This was achieved without medication use (complete success) in 62.5%, 71.7%, and 73.0% percent of eyes, respectively. Qualified success was achieved in 77.6%, 81.6%, and 84.2% of eyes.

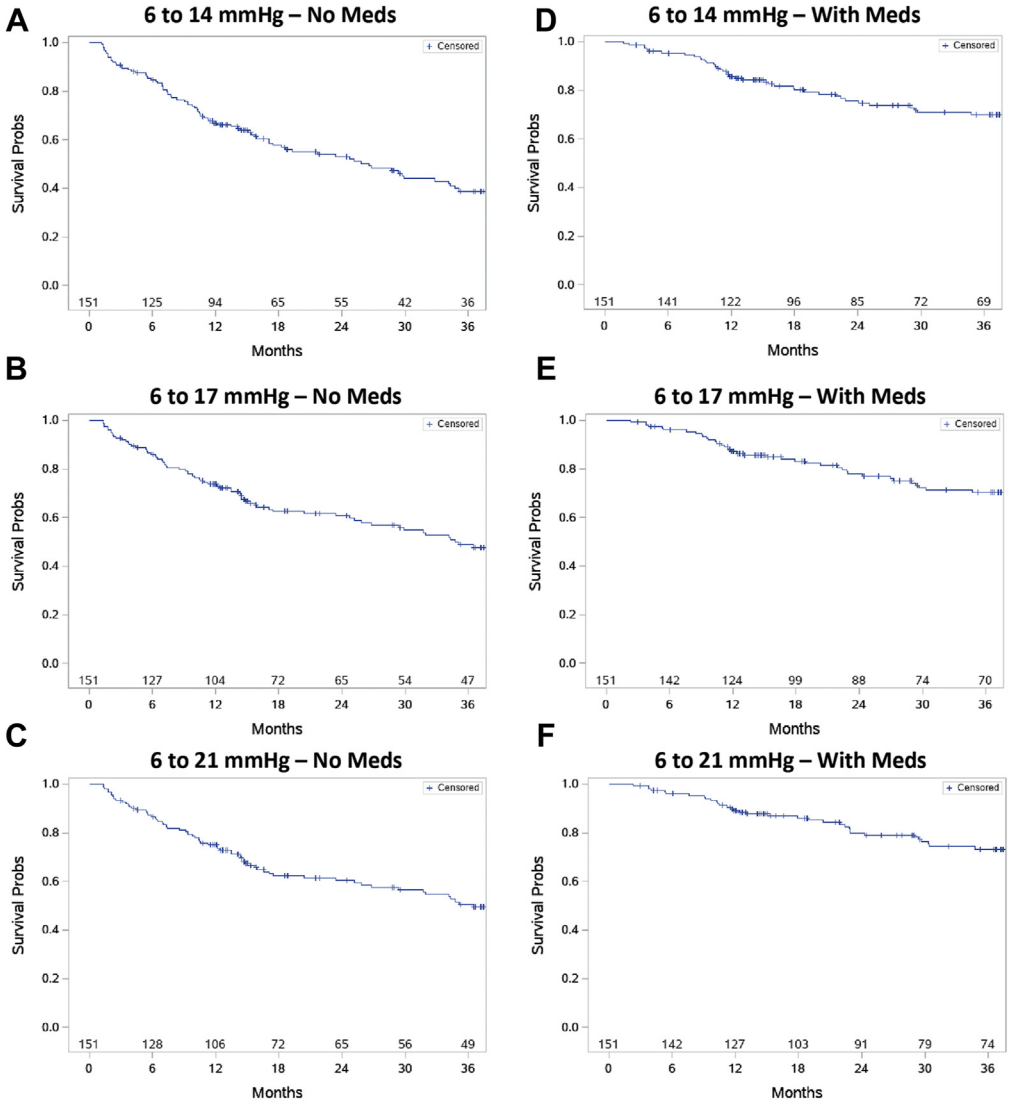

Figure 1. Kaplan–Meier survival curves for complete and qualified success through 36 months. **A**–**C**, Kaplan–Meier survival curves for complete success defined as patients being medication free, achieving a ≥ 20% IOPR, and within one of the following IOP ranges: **A**, 6 to 14 mmHg, **B**, 6 to 17 mmHg, **C**, 6 to 21 mmHg. **D**–**F**, Qualified success was defined as patients requiring medications to achieve a ≥20% IOPR and one of the following IOP ranges: **D**, 6 to 14 mmHg, **E**, 6 to 17 mmHg, **F**, 6 to 21 mmHg. IOP = intraocular pressure; IOPR = intraocular pressure reduction.

Characteristics Associated with Surgical Failure

For the Cox regression analysis identifying risk factors for failure (Fig 3), we used the 6 to 17 mmHg IOP cutoff with ≥ 20% intraocular pressure reduction (IOPR) from baseline. Kaplan–Meier curves for selected variables are depicted in Figures S4 and S5 (available at www.ophthalmologyglaucoma.org). Receiving an intraoperative MMC dose < 0.4 mg/ml had a higher risk of failure on a univariable basis (hazard ratio [HR], 2.14; 95% CI, 1.34–3.41). In the adjusted multivariable analysis, receiving a MMC dose of < 0.4 mg/ml (HR, 2.42; 95% CI, 1.44–4.05) remained a significant risk factor for failure, and having a baseline IOP lower than 21 mmHg was a statistically significant risk factor for failure (HR, 1.79; 95% CI, 1.03–3.13). The clustering effect of some patients having 2 eyes enrolled in the study did not significantly impact outcomes; Figure 3 demonstrates no changes to the conclusions drawn from the original adjusted multivariate model in comparison to the fragility model.

Primary open-angle glaucoma, ethnicity, left eye, female sex, poor preoperative vision, diabetes, age < 70 years, previous trabeculoplasty, MD less than −12 dB on visual field testing, and pseudophakia all had insufficient evidence to support prognostic utility. Having a baseline IOP lower than 21 mmHg violated the proportional hazards assumption; however, the correlation coefficient of the time-variable interaction term was < 1% so this interaction was not corrected. Instead, the multivariate model was adjusted through stratification based on having a baseline IOP lower than 21 mmHg. No variables were impacted by collinearity, and there was no significant effect of surgeon learning curve on

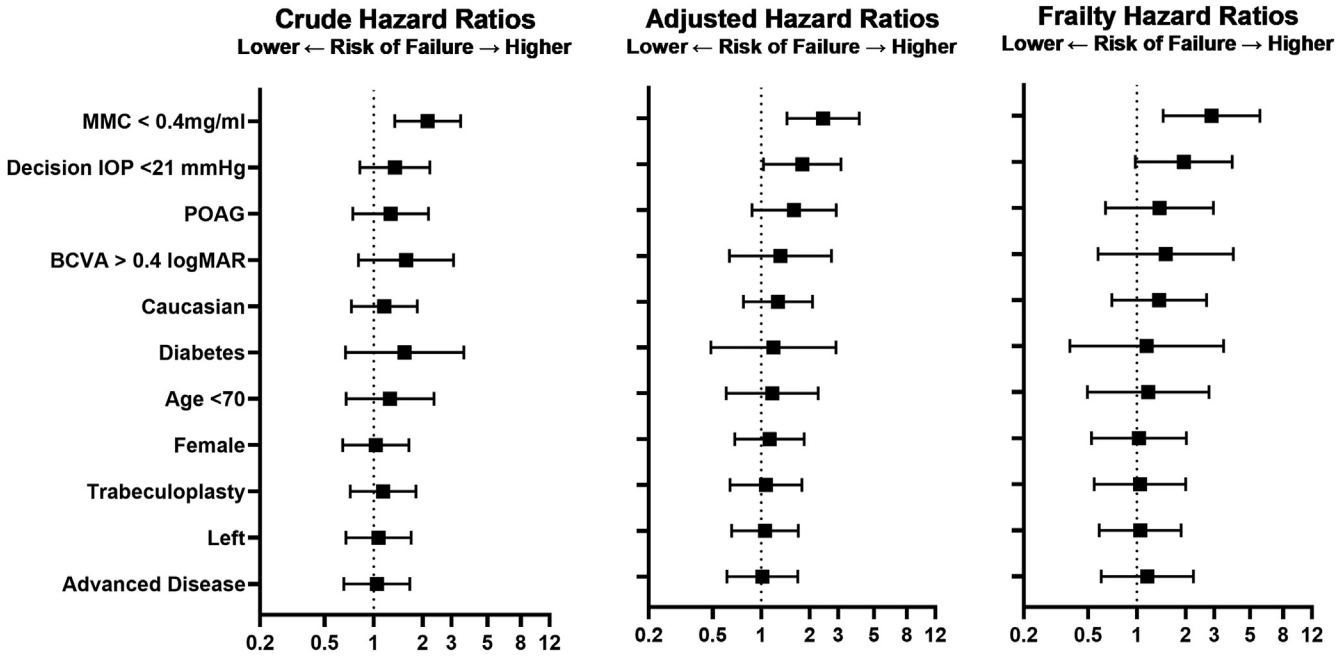

Figure 3. Results from a Cox proportional hazards model, based on the following success criteria: (1) no 2 consecutive IOP readings greater than 17 mmHg, nor clinical hypotony (defined as: IOP less than 6 mmHg with more than 2 lines of vision loss from baseline); (2) at least a 20% reduction from preoperative IOP; and (3) no glaucoma medication use. Shown are crude (Left), multivariate adjusted (Center), and frailty model (Right) hazard ratios for various risk factors, with 95% confidence intervals. Decision IOP: intraocular pressure at the time surgery was decided. Advanced glaucoma was defined as a mean deviation on visual fields worse than −12 dB. IOP = intraoperative pressure; MMC = mitomycin C; POAG = primary open-angle glaucoma.

success rates between the first one-third of surgeries and the latter two-thirds of surgeries (HR, 1.44; 95%CI, 0.58−3.6; Table S4, available at www.ophthalmologyglaucoma.org).

Outcomes Based on Preoperative Visual Field Disease Severity

Complete success was attained in 50.3% of patients and qualified success in 70.4% of patients after 3-years follow-up (Fig S6, available at www.ophthalmologyglaucoma.org). A Cox proportional hazards model based on this outcome revealed, in the adjusted multivariable analysis, that receiving a MMC dose of < 0.4 mg/ml (HR, 2.88; 95% CI, 1.72−4.81) was a significant risk factor for failure and having a baseline IOP lower than 21 mmHg was a significant risk factor for failure (HR, 1.85; 95% CI, 1.08−3.15). Again, the outcomes were not significantly impacted by the clustering effect of some patients having 2 eyes enrolled in the study.

Intraocular Pressure, Medication Use, and Best-corrected Visual Acuity

At baseline, the median IOP was 20.0 mmHg (IQR, 16−26 mmHg) and the median medication use was 4 (IQR, 3−4). At 3 years, the median IOP was 12.4 mmHg (IQR, 10−15.5 mmHg) and the median medication use was 0 (IQR, 0−2) censoring for reoperations (Fig 7). An individualized representation of patient IOP changes from the decision for microshunt implantation to the first reported visit 3-years postoperatively is demonstrated in Figure 8.

Dividing the eyes by < 0.4 mg/ml intraoperative MMC dose, there was a statistically significant difference in IOPs 3 years postoperatively ($P = 0.01$) with eyes receiving < 0.4 mg/ml MMC achieving median 14.0 (IQR, 11−16) mmHg and eyes receiving ≥ 0.4 mg/ml achieving a lower median of 12.0 (IQR, 10−14) mmHg. There was also a statistically significant difference in medication use ($P = 0.002$) with eyes receiving < 0.4 mg/ml MMC requiring median of 1 (IQR, 0−2) medication and eyes receiving ≥ 0.4 mg/ml requiring a median of 0 (IQR, 0−1) medications 3 years postoperatively.

A patient-level representation of medication changes from baseline to 3-years follow-up is presented in Figure 9. At 3 years, 57 (59.4%) eyes were glaucoma medication free. At last follow-up, 102 (67.1%) eyes were medication free. Time to first postoperative medication use is presented in Figure S10 (available at www.ophthalmologyglaucoma.org) and occurred a median (IQR) of 16.9 (12.1−34.1) months after surgery. Eyes with primary open-angle glaucoma and patients experiencing IOP >10 mmHg within the first postoperative month were more likely to start medications earlier during follow-up ($P = 0.02$ and $P = 0.01$, respectively). Of eyes that achieved qualified success, at 3 years, 86.8% were on fewer medications than at the time the decision was made for surgery; 11.2% were on the same, and 2.0% were on more.

The median (IQR) best-corrected visual acuity went from 0.18 (0.1−0.3) logMAR at baseline to 0.18 (0.1−0.3) logMAR at 3 years ($P = 0.14$), with 131 (86.2%) eyes maintaining baseline vision or better. Sixteen (10.5%) eyes lost more than 2 lines of vision at last follow-up or reoperation. There was no significant difference in final visual outcomes between patients receiving higher or lower intraoperative doses of MMC ($P = 0.34$). Time to recovery of preoperative vision is presented in Figure S11 (available at www.ophthalmologyglaucoma.org). Risk factors for

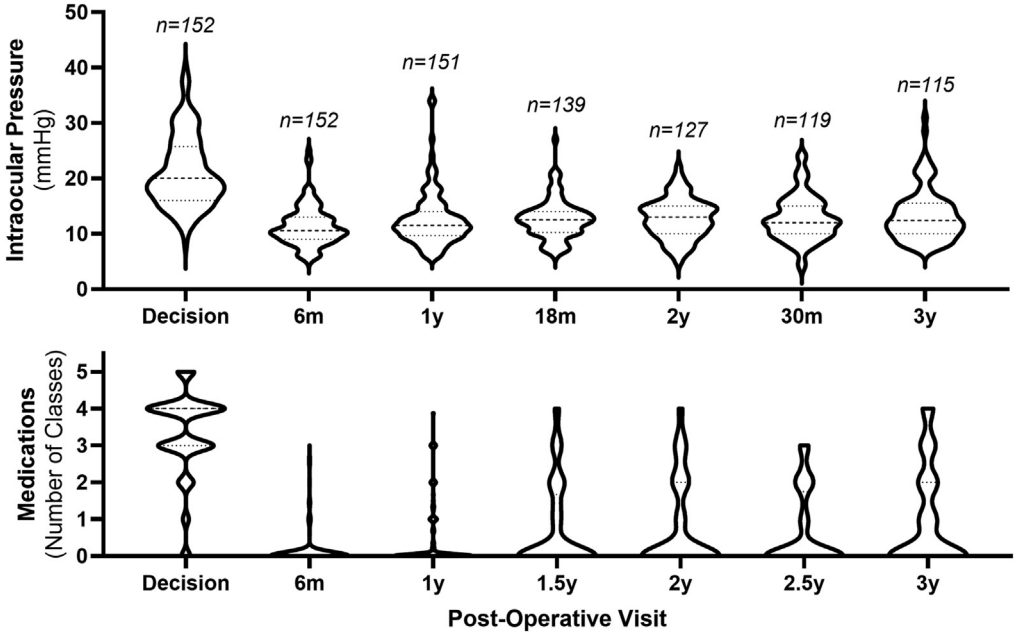

Figure 7. Violin plots with median and interquartile ranges of intraocular pressure and medication classes at the time the decision was made to undergo surgery and at the indicated follow-up visit. The depicted data were censored for patients with reoperations (n = 14). Width of the violin plots represents the proportion of patients at a given y-value at each follow-up visit.

slower visual recovery included preoperative vision better than or equal to 0.4 logMAR (HR, 2.13; 95% CI, 1.27−3.56) and phakic lens status (HR, 1.59; 95% CI, 1.12−2.25) on a univariable basis. On a multivariable basis, preoperative vision better than or equal to 0.4 logMAR (HR, 2.65; 95% CI, 1.52−4.63), baseline IOP greater than 21 mmHg (HR, 1.49; 95% CI, 1.02−2.17), and phakic lens status (HR, 1.76; 95% CI, 1.22−2.55) were statistically significant risk factors.

Complications

Forty-four eyes (28.9%) had a total of 55 complications (Table 5), occurring with the highest frequency during the first postoperative month. The median (IQR) time to first complication after the first month was 15.2 (12.6−25.5) months (Fig 12A, B). No eyes experienced persistent clinical hypotony with associated vision loss. Early choroidal detachments all resolved with conservative management (involving topical steroids and atropine 1%) except in 2 cases that required viscoelastic AC reformation. One eye received posterior sub-Tenon triamcinolone acetonide injection (40 mg/ml × 0.2 ml) for persistent late choroidal detachment. All choroidal detachments resolved before 6 months. There were 2 cases of persistent significant corneal edema that underwent further intervention, both with pre-existing corneal problems before SIBS microshunt implantation. One eye had known poor corneal endothelial health preoperatively (endothelial cell density: 794 cells/mm^2) and developed corneal edema 17.5 months postoperatively, which was treated with Descemet stripping automated endothelial keratoplasty (DSAEK) 2 years after SIBS microshunt implantation. The second case also had known poor corneal endothelial health before surgery (545 cells/mm^2) and developed corneal edema 1.5 years postoperatively, which improved after receiving a 2-week course of sodium chloride hypertonic eye drops. No eyes experienced significant complications of loss of light perception vision, retinal detachment, angle closure, malignant glaucoma, microshunt erosion, blebitis, or endophthalmitis. No significant differences in overall complication rate were apparent among eyes that received different intraoperative MMC concentrations (chi squared, $P = 0.07$). When only hypotony related complications such as IOP < 6 mmHg and/or choroidal detachment are considered, no significant differences in postoperative rates were apparent among eyes receiving different intraoperative MMC concentrations (chi squared, $P = 0.21$).

Postoperative Interventions

There was a total of 53 distinct interventions in 31 eyes (20.4%) (Table 6). Many eyes had multiple interventions, however digital ocular compression, ptosis repair, and yttrium aluminum garnet capsulotomy were always performed in eyes that also had additional interventions. The most common intervention was needling (15.1%), followed by AC injection (3.3%) or tap (1.9%). Eyes receiving less than 0.4 mg/ml MMC intraoperatively received postoperative interventions more frequently (38.1% vs. 40.4%); however, this was not statistically significant (odds ratio, 1.1; 95% CI, 0.56−2.22).

Characteristics Associated with Receiving Needling

Needling numbers were modest (n = 23 eyes; 15.1%), with 2 patients receiving a second needling. A baseline IOP > 21 mmHg was significantly associated with a higher rate of needling (HR, 3.21; 95% CI, 1.38−7.48) in the univariate analysis, which remained significant in the multivariate analysis (HR, 3.04; 95%CI, 1.21−7.64) (Figure S13, available at

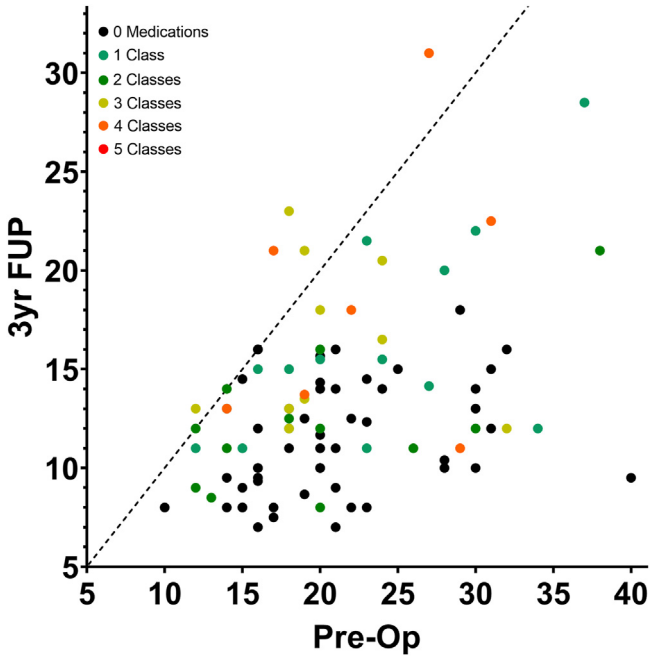

Figure 8. Scatterplot of intraocular pressure (IOP) at the time of surgical decision (x-axis) vs. the IOP at postoperative year 3 (3yr FUP; y-axis). The points represented are measurements taken at the closest visit to 36 months postoperatively between 33 months and 39 months. Patients without available data in this range were not represented in this chart. The color of the data point represents a patient's medication requirement at 3 years. Data points plotted along the dotted line represent no change in IOP from the time surgery was decided to postoperative month 36, and all those under the dotted line represent a reduction from the decision IOP.

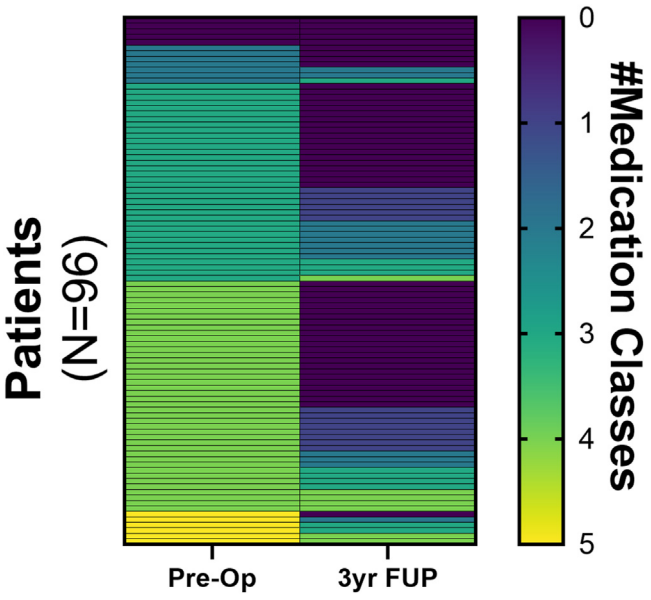

Figure 9. Heatmap representing the percentage of patients' eyes on 0 to 5 glaucoma medication classes at the time of surgical decision and at postoperative year 3.

www.ophthalmologyglaucoma.org). The mean and median time to needling was 19.5 and 11.3 months, respectively. Mean and median IOP were 23.0 mmHg and 20.0 mmHg, and number of medications was 1.9 and 2, respectively. Intraoperative dose of MMC was not associated with receiving needling.

Reoperation and Revisions

Eleven eyes (7.2%) experienced a revision at a median (IQR) of 16.9 (13.5−24) months postoperatively (Table 7). Two eyes underwent bleb revision alone. Nine eyes received a bleb revision with a new SIBS microshunt implanted in the same location, and one of these patients received a subsequent bleb revision approximately 8 months later. Subsequent follow-up in these patients was uneventful. Receiving <0.4mg/ml intraoperative MMC was associated with an increased risk of experiencing ab externo bleb revision with device exchange (odds ratio, 4.9; 95% CI, 1.3−18.3).

Four eyes (2.6%) underwent a reoperation for glaucoma at a median (IQR) of 15.8 (12.6−19.6) months postoperatively (Table 7). Three received a Baerveldt glaucoma implant (Johnson and Johnson Surgical Vision, Inc) because of persistent IOP elevation above 30 mmHg on 3 medication classes, and one received an Ahmed glaucoma valve (New World Medical, Inc) after 2 failed needling attempts, with an IOP of 23 mmHg on 5 medication classes.

Discussion

This study presents the postoperative clinical course of 152 consecutive glaucomatous eyes on maximally tolerated medical therapy undergoing stand-alone SIBS microshunt implantation as a primary subconjunctival glaucoma surgical intervention. It is the largest study to date reporting 3-year surgical outcomes. By the end of follow-up, complete and qualified success (upper threshold of 17 mmHg) was achieved in 55.6% and 74.8% of eyes, respectively. Fifty-nine percent of patients were medication free, and there was a median medication reduction of 3 classes. Needling occurred in 15% of eyes, and 3% required additional glaucoma surgery. Most notably, receiving an intraoperative MMC dose < 0.4 mg/ml was significantly associated with surgical failure and ab externo bleb revision with device exchange in this study's population.

The primary and secondary outcomes for surgical success utilized by the present study follow those updated by the World Glaucoma Association in 2018[17] and are commonly associated with the Tube versus Trabeculectomy studies.[18,19] Based on these standard criteria, prior retrospective studies on the SIBS microshunt collectively report success rates based on an IOP threshold of ≥6 and ≤17 mmHg that range from approximately 25% to 100% over 1 to 5 years follow-up,[9,12] with most frequent complications being clinically insignificant hypotony (IOP <6 mmHg, but no corresponding visual dysfunction), increased IOP requiring intervention, as well as subconjunctival bleeding and hyphema.[9,10,12,13,15] The present study's findings, using equivalent success criteria, sit squarely in the middle of this range, and report similar complication types and rates. In line with previous studies,

Table 5. Microshunt Eyes with Postoperative Complications

Complication	Total, n = 44 (28.9%) (N = 152 Eyes)	
	Early (< 1 mo) N = 23 Eyes (15%)	*Late (≥ 1 mo) N = 21 Eyes (14%)*
Any complication		
Choroidal detachment	10 (7%)	2 (1%)
Hyphema	8 (5%)	1 (1%)
Shallow anterior chamber	8 (5%)	0
Leak/dehiscence	1 (1%)	1 (1%)
Monocular diplopia	1 (1%)	1 (1%)
Vitreous hemorrhage	1 (1%)	0
Binocular diplopia	0	7 (5%)
Bleb encapsulation	0	0
Blocked lumen	0	1 (1%)
Hypotony maculopathy	0	1 (1%)
Iritis	0	3 (2%)
Macular edema	0	2 (1%)
Persistent corneal edema	0	2 (1%)
Ptosis	0	2 (1%)
Tube migration	0	1 (1%)
Serious complications		
Angle closure	0	0
Blebitis/endophthalmitis	0	0
Malignant glaucoma	0	0
No light perception	0	0
Retinal detachment	0	0

clinically significant hypotony was largely avoided and only one tube migration occurred.

The surgical success rates we report 3 years after SIBS microshunt implantation also compare favorably with previously reported 3-year surgical success rates after traditional trabeculectomy. The Primary Tube Versus Trabeculectomy (PTVT) study reported a qualified success rate of 72% at 3 years using identical criteria to our primary outcome with an upper IOP threshold of 17 mmHg. The PTVT study also employed an upper IOP threshold of 21 mmHg to report a 44% complete success rate and 71% qualified success rate.[18] With identical success criteria, Ehrnrooth et al[20] reported 45% complete and 64% qualified success rates 3 years after trabeculectomy. Applying similar success criteria to our SIBS microshunt cohort, we find a complete success rate of 57% and a qualified success rate of 77%, suggesting more favorable outcomes can be attained with the SIBS microshunt. However, well designed randomized studies are necessary to fully elucidate the differences in clinical outcomes between these devices.

A recent randomized controlled trial comparing the SIBS microshunt to traditional trabeculectomy revealed the SIBS microshunt to be slightly yet significantly inferior to trabeculectomy in terms of postoperative success at 1 year.[15] Twelve percent more patients in the trabeculectomy arm achieved success compared with the SIBS microshunt arm; however, patients in the trabeculectomy group experienced a significantly higher rate of postoperative hypotony, incidence of elevated IOP requiring treatment, and significantly more complications leading to reoperation. It is notable that there were significantly more Black patients in the SIBS microshunt group compared with the trabeculectomy group. When the SIBS microshunt arm of this randomized controlled trial (RCT) is compared with the present study using an equivalent IOP threshold of $\leq$ 21mmHg (with medications, without clinical hypotony, loss of light perception, or reoperation), the presented cohort reports a higher rate of surgical success at 3 years (approximately 77.5% success) compared with the 1-year outcomes (approximately 65% success) reported by the RCT. In addition to the well-known confounders impacting comparisons between different study designs and populations, it is important to note that this RCT employed a prespecified IOP threshold for reintroduction of glaucoma medications. Such a study design may serve to increase the failure rate compared with the present study as medication use comprises part of the surgical success criteria. Also, our present study included higher intraoperative MMC concentrations (0.2−0.5 mg/ml) which may have contributed to a higher rate of surgical success.

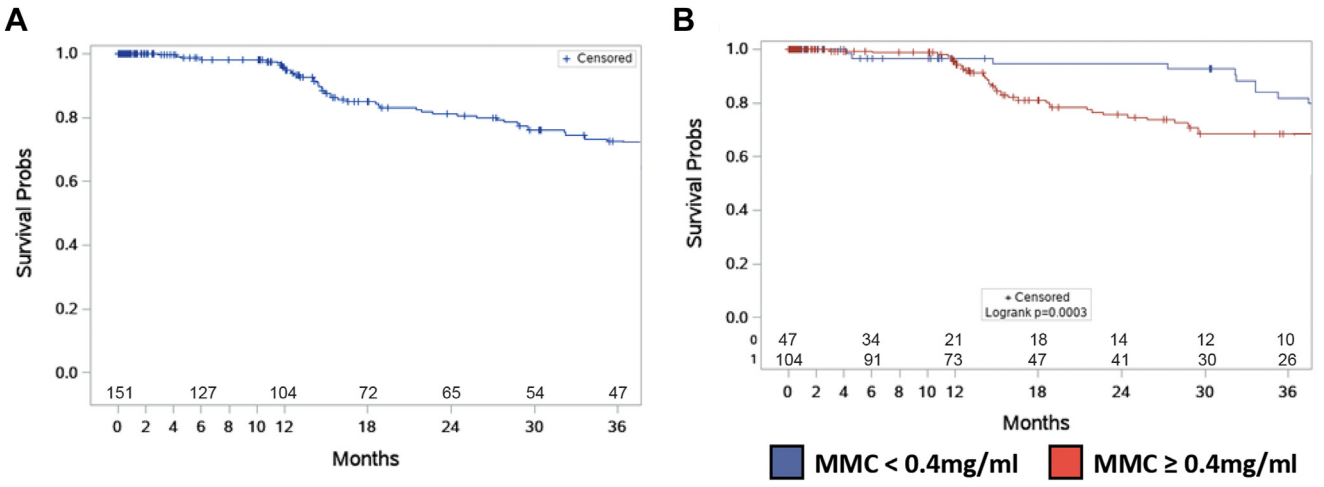

Figure 12. Kaplan−Meier survival curves for **A**, any postoperative complication (after the first postoperative month), and **B**, postoperative complications stratified MMC dose ≥ 0.4 mg/ml. MMC = mitomycin C.

Table 6. Microshunt Eyes with Postoperative Interventions

Intervention	Total, n (%) (N = 152 Eyes)	MMC < 0.4 mg/ml (N = 47 Eyes)	MMC ≥ 0.4 mg/ml (N = 105 Eyes)	OR (95% CI)
Needling	23 (15%)	11 (23%)	12 (11%)	0.42 (0.18–1.04)
Second needling	2 (1%)	0	2 (2%)	n/a
MMC injection	9 (6%)	4 (9%)	5 (5%)	0.54 (0.15–1.83)
OVD injection	9 (6%)	4 (9%)	5 (5%)	0.54 (0.15–1.83)
Second injection	1 (1%)	0	2 (2%)	n/a
5-FU injection	1 (1%)	0	1 (1%)	n/a
AC injection	5 (3%)	1 (2%)	4 (4%)	0.55 (0.04–3.48)
AC tap	3 (2%)	0	3 (3%)	n/a
Second AC tap	1 (1%)	0	1 (1%)	n/a
Other (digital ocular compression, ptosis repair, YAG capsulotomy)	30 (20%)	8 (17%)	22 (21%)	0.77 (0.33–1.80)

AC = anterior chamber; CI = confidence interval; 5-FU = 5-fluorouracil; IOP = intraocular pressure; MMC = mitomycin C; OR = odds ratio; OVD = ophthalmic viscoelastic device; YAG = yttrium aluminium garnet.

Although lower doses of MMC (i.e., 0.2 mg/ml) are known to be viable for traditional surgical approaches in the subconjunctival space, the SIBS microshunt is positioned relatively deeper and lies within the "sub-Tenon's" space. Variations in fibroblast density, extracellular matrix composition, and stiffness are known to exist between Tenon's capsule and the more superficial subconjunctival tissues,[21–23] suggesting that different concentrations of intraoperative MMC may be required to achieve the same anti-proliferative effect. Furthermore, surgeon learning curve and surgical technique for the microshunt may have had a role in the reduced success rate found in this RCT.

The Cox proportional hazards analysis in the present study failed to identify many of the factors traditionally associated with surgical failure (i.e., race, diabetes, age)[24,25] as significant predictors of surgical success. However, higher baseline IOP was identified as a significant risk factor, which corroborates previous work reporting baseline IOP to be significantly predictive of outcomes in other subconjunctival bleb-forming surgeries.[26,27] Patients that received intraoperative MMC concentrations below 0.4 mg/ml were approximately twice as likely to experience surgical failure. These findings agree with previously published work[10,13,14] and collectively lend strong support to the use of intraoperative MMC concentrations $\geq$ 0.4 mg/ml.

Despite having a longer follow-up period, substantially fewer complications were observed in the present study compared with those published previously on the SIBS microshunt, with most reporting early and late complication rates ranging from 35% to 60% compared with just under 30% in the current study.[9,10,12,13] The most common complication in the current study was choroidal detachment (n = 12; 7%), a rate slightly higher than previous reports ranging from 2% to 5%.[9,10] Subconjunctival bleeding or hyphema occurred in 6% of eyes and at a similar rate to previous reports ranging from 2% to 23%.[13,15] Prior SIBS microshunt cohorts reported bleb leaks in 4% to 7% of cases,[13,15] substantially higher than the 2% of cases observed in the present study. Given that the PTVT study reported an overall 3-year complication rate of 48% after trabeculectomy,[18] the 30% rate reported in the present SIBS microshunt cohort appears quite favorable and may be explained by the relatively lower number of wound leaks and bleb encapsulations observed in the presented SIBS microshunt cohort compared with those observed in the trabeculectomy arm of the PTVT study. However, caution is warranted when

Table 7. Eyes with Postoperative Revisions and Reoperations

Procedure	Total, n (%) (N = 152 Eyes)	MMC < 0.4 mg/ml (N = 47 Eyes)	MMC ≥ 0.4 mg/ml (N = 105 Eyes)	OR (95% CI)
Any revision	11 (7%)	6 (13%)	5 (5%)	2.9 (0.8–9.0)
Ab externo microshunt bleb revisions with device exchange	9 (6%)	6 (13%)	3 (3%)	4.9 (1.3–18.3)
Ab externo microshunt bleb revisions	2 (1%)	+−	2 (2%)	−
Any reoperation	4 (3%)	2 (4%)	2 (2%)	2.3 (0.3–14.9)
Ahmed Glaucoma Valve	1 (1%)	−	1 (1%)	−
Baerveldt glaucoma implant	3 (2%)	2 (4%)	1 (1%)	4.6 (0.6–68)

CI = confidence interval; MMC = mitomycin C; OR = odds ratio.

comparing complication rates between studies of different follow-up durations and study designs (randomized vs. nonrandomized).

The overall postoperative intervention rate was 40% over 3 years in the current study, which is consistent with previous reported rates after SIBS microshunt of 36% to 40% over follow-up periods ranging from 1 to 3 years. Previous studies report needling rates after SIBS microshunt implantation of 5% to 19% over 2 to 3 years of follow up[9,15]; the presented cohort complements these data with needling occurring in 15% of eyes at a mean of 19.5 months postoperatively. In the present study, patients with a baseline IOP $>$ 21 mmHg were approximately 3 times as likely to undergo needling, which is in line with previous findings after gelatin microshunt implantation that associates increased needling rates with elevated preoperative IOPs.[28]

Previous studies on the SIBS microshunt report surgical revisions occurring in 5% to 10% of cases over follow-up periods ranging from 1 to 3 years,[9,13] with 7% of eyes undergoing revisions in the present study after 3 years. Further, use of intraoperative MMC concentrations less than 0.4 mg/ml was significantly associated with a higher rate of ab externo bleb revision with device exchange. However, rates of reoperation for glaucoma were not significantly higher in patients that received lower concentrations of intraoperative MMC. In fact, reoperations were relatively infrequent within the presented cohort, with only 3% of eyes requiring a second glaucoma surgery. Previous studies report higher reoperation rates, ranging from 7% to 17% of eyes.[9,13]

The SIBS microshunt, with its unique design and minimally invasive approach, is positioned to mitigate surgical risk and postoperative management compared with traditional glaucoma surgeries. Our results show a low rate of clinical hypotony, and we observed a tendency for the observed cases of transient hypotony to spontaneously resolve without major interventions. In cases presenting with transient hypotony, we would recommend observation and cycloplegia if choroidal detachments are present. If clinical hypotony remains unresolved, air injection, viscoelastic injection, bleb compression sutures, or bleb cautery could be considered. In our study, needling was our preferred option before adding glaucoma medications, except when patient preferences did not align or if signs of bleb hyper encapsulation or avascularity were present. If a surgical revision was indicated, our preferred approach was a bleb revision if the conjunctiva was amenable.

The surgical technique was consistent across the eyes, except for the intraoperative MMC dose administered. As previously mentioned, MMC dosing was increased as surgeons became increasingly comfortable with the microshunt bleb morphology. Initially the blebs were found to be posterior with minimal avascularity, leading to an increase in MMC concentration from 0.2 mg/ml to 0.4 mg/ml and 0.5 mg/ml. In addition, a careful tissue dissection (separating tenon from conjunctiva), meticulous placement of the device under the tenon capsule, and 2-step wound closure seem to improve the microshunt bleb morphology. As clinical experience with the device increases, a refinement of the surgical technique and a better understanding of the ideal postoperative management regimen is expected, improving functionality and optimizing surgical outcomes.

Limitations of this study include the noncomparative and nonrandomized nature and the fact that results likely capture at least part of the surgical "learning curve" inherent to novel surgical devices and procedures; however, no significant difference in success was found between the first one-third of surgeries and the latter two-thirds. External generalizability is always an open question across different surgeons, sites, and patient populations. Many retrospective studies suffer from significant loss to follow-up, which may be differential, although in this cohort our loss to follow-up was minimal considering the 3-year follow-up period (75% had 36-month follow-up) and was nondifferential between comparison groups. Further, the baseline characteristics of those lost to follow-up were very similar to those with complete follow-up, save for significantly higher doses of intraoperative MMC in those lost to follow-up. As higher doses of MMC were associated with longer event-free survival time, this significant difference in baseline characteristics may have resulted in a slight underestimation of reported success rates. Gaps in follow-up and shared patient care make adequately evaluating device safety challenging, despite a sample size comparable to other major trials in the glaucoma surgical space. This is a continuing issue for new medical devices. All the same, the low complication rates reported in this study are encouraging. Finally, IOP is an imperfect measure of glaucoma control. Structural and/or functional testing would ideally be utilized to better capture differential glaucoma progression rates after surgery as ultimately the most meaningful clinical outcome; however, defining surgical success in glaucoma studies will remain an ongoing challenge.[29]

New innovations also must be analyzed from a cost-effectiveness perspective, which was beyond the scope of this study. Although a trabeculectomy is less expensive at the time of surgery because it does not require an implant, the bulk of associated care costs stem from postoperative visits and the management of complications/failures.[30] Ultimately the total cost of the surgery and follow-up should be considered, including the frequency of follow-up visits, number of interventions (i.e., needling, and in some renumeration systems laser suture lysis is a billable procedure), value gained in quality adjusted life years (patient experience), cost of remaining medication requirements, reoperations, and ultimately, permanent visual disability that may occur after surgery. Reducing the incidence and impact of surgical complications and failures will likely incentivise the shift of surgical treatment ever earlier in the glaucoma treatment algorithm.

In conclusion, 3-year follow-up data after ab externo SIBS microshunt implantation demonstrate high rates of qualified and complete success, decreased glaucoma medication requirements, few complications, infrequent postoperative interventions, and a low rate of reoperation. Glaucoma surgeons and healthcare professionals involved in the management of surgical glaucoma patients will benefit

from understanding that the presented data support use of intraoperative MMC concentrations $\geq$ 0.4 mg/ml and substantiate earlier reports of this promising new procedure in the continually evolving field of glaucoma surgery.

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Abbreviations and Acronyms:
AC = anterior chamber; **CAI** = carbonic anhydrase inhibitor; **CI** = confidence interval; **DSAEK** = Descemet stripping automated endothelial keratoplasty; **HR** = hazard ratio; **IOP** = intraocular pressure; **IOPR** = intraocular pressure reduction; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **MD** = mean deviation; **MMC** = mitomycin C; **OAG** = open angle glaucoma; **POAG** = primary open angle glaucoma; **PTVT** = Primary Tube Versus Trabeculectomy; **PXG** = pseudoexfoliation glaucoma; **RCT** = randomized controlled trial; **SIBS** = poly(styrene-block-isobutylene-block-styrene).

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Glaucoma surgery, Microshunt, SIBS, Subconjunctival filtering, Trabeculectomy.

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